REMARKS

Applicants thank the Examiner for considering the amendments and response filed on November 30, 2006. Claims 47-52 and 54-63 are pending in this application. Claims 47 and 62 are amended; claim 53 is canceled. The amendments are of a formal nature and do not add new matter. All amendments and cancellations are made without prejudice or disclaimer. Applicants reserve the right to pursue canceled or amended subject matter in this or related patent applications.

WITHDRAWAL OF REJECTIONS/OBJECTIONS

Applicants acknowledge withdrawal of the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 88-109 of co-pending Application No. 09/863,693 due to the abandonment of 09/863,693.

Applicants acknowledge withdrawal of the rejection of claims 47-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicants acknowledge withdrawal of the rejection of claims 59, 60, and 63 under 35 U.S.C. 102(b), as being anticipated by Hu (Hu, S. et al., Cancer Res. 56: 3055-3061, 1996).

Applicants acknowledge withdrawal of the rejection of claims 54, 56 and 58 under 35 U.S.C. 102(b), as being anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994) as evidenced by Merchant (Merchant, A.M. et al., Nature Biotechnology, 16: 677-681, 1998).

Applicants acknowledge apparent withdrawal of the rejection of claims 54 and 58 under 35 U.S.C. 102(b), as being anticipated by de Kruif (de Kruif et al., Jour. Biol. Chem., 271(13): 7630-34, 1996) as evidenced by Merchant (*supra*).

DOUBLE PATENTING

Applicants acknowledge the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 30-38, 40-43, 45-51 and 53-55 of co-pending Application No. 09/373,403. Applicants request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 45-82 of co-pending Application No. 10/143,437, now U.S. Patent No. 7,183,076. Applicants request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

Applicants also wish to bring to the Examiner's attention the following currently co-pending patent applications: U.S. application serial no. 11/537,195, U.S. application serial no. U.S. application serial no. 11/608,673, U.S. application serial no. 11/536,951, and U.S. application serial no. 11/536,439. Applicants request that the Examiner hold any further double-patenting rejections in abeyance until notice of allowable subject matter.

CLAIM REJECTIONS 35 U.S.C. § 112

Applicants acknowledge the rejection of claim 53 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully submit the rejection is moot as the claim has been canceled.

CLAIM REJECTIONS 35 U.S.C. § 102

Applicants acknowledge the Examiner maintained the rejection of claims 47, 52 and 53 under 35 U.S.C. § 102(b) as allegedly anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994) as evidenced by Merchant (Merchant, A.M. et al., Nature Biotechnology, 16: 677-681, 1998). Applicants note that claim 53 is canceled and so the rejection as it applies to claim 53 is moot.

The Examiner rejected claims pending 47 and 52 under 35 U.S.C. § 102(b) as allegedly anticipated by Nissim. The Examiner stated that Nissim teaches methods for expressing scFv fragments in E. coli from a phage library, and that Merchant teaches that the phage library of Nissim has extensive H chain repertoires but a unique L chain sequence. The Examiner argued that the bispecific antibodies of claims 47 and 52 (and 53) do not necessarily comprise separate multimerization domains. Thus, the Examiner argued that these claims read on diabodies where the interaction between two scFvs is via the heavy and light chain variable domains, where diabodies are formed by the binding of a light chain variable domain from one scFv binding with a heavy chain variable domain of a second scFv. Therefore, the Examiner alleged that Nissim's "polyclonal" multimerized products are bispecific.

Applicants respectfully disagree with the Examiner's characterization of Nissim. Nissim discloses scFvs where a single peptide backbone comprises both the heavy chain variable region and light chain variable region. Nevertheless, while not acquiescing to the rejection and solely to expedite prosecution, claim 47 now indicates that the light chain variable region ("monomer") is on a separate polypeptide backbone from the heavy chain variable region; *see*, for example, paragraph 0029 of the specification as well as Figure 1C. Applicants respectfully submit that the rejection therefore does not apply to the current claims. Withdrawal of the rejection is respectfully requested.

Applicants acknowledge the rejection of claims 47, 48, 50, 52 and 53 under 35 U.S.C. § 102(b) as allegedly being anticipated by de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant, *supra*. Applicants note that claim 53 is canceled and so the rejection as it applies to claim 53 is moot.

The Examiner alleged that de Kruif teaches a method for making bispecific scFv antibodies that contain IgG3 hinge regions and either a Fos or Jun leucine zipper connected to the scFv proteins, and also with cysteine residues incorporated into the leucine zippers. Such nucleic acids encoding such dimerization regions are placed in frame with scFvs isolated from libraries. One of several libraries listed is the Nissim library (supra). The Examiner's position is that Merchant teaches that the Nissim has an extensive H chain repertory and a unique L chain sequence. Therefore, the Examiner concludes that de Kruif provides bispecific antibodies that are the same as that claimed in claims 47, 48, 50 and 52 (and 53).

Applicants respectfully disagree with the Examiner's characterization of de Kruif. de Kruif only discloses scFvs where a single peptide backbone comprises both the heavy chain variable region and light chain variable region by referencing the Nissim library. de Kruif does not teach any advantage of using the same light chain and only mentions the Nissim library as one of a listing of possible libraries that could be used. Nevertheless, while not acquiescing to the rejection and solely to expedite prosecution, claim 47 now indicates that the light chain variable region ("monomer") is on a separate polypeptide backbone from the heavy chain variable region (*see*, for example, paragraph 0029 of the specification as well as Figure 1C). Applicants respectfully submit claims 47, 48, 50, and 52 are clearly not anticipated by de Kruif, therefore, withdrawal of the rejection is respectfully requested.

CLAIM REJECTIONS – 35 U.S.C. § 103

Applicants acknowledge the rejection of claims 47-49, 52-55, 58-61 and 63 under 35 U.S.C. § 103(a) as allegedly being unpatentable over de Kruif, *supra*, as evidenced by Merchant, *supra*, in view of Ridgway (of record) "for the reasons of record." Applicants note that claim 53 is canceled and so the rejection as it applies to claim 53 is moot.

The Examiner categorizes claims 47-49, 52, 54, 55, 58-61 and 63 as including within their scope bispecific antibodies that contain engineered C_H3 domains, where the first and second polypeptides interact at an amino acid side chain protuberance of one polypeptide and an amino acid side chain cavity of the other polypeptide. de Kruif is applied as in the previous rejection. The Examiner acknowledges that the protuberance and cavity interaction is not taught by de Kruif, but asserts that, as evidenced by Ridgway, the "knobs-into-holes" strategy was used to successfully enhance the production of bispecific diabodies (at p. 620, last paragraph). The significance of Merchant is not explained in the present rejection, but based on the rejection under 35 U.S.C. § 102(b) above and the previous Office Action, it appears that it is cited as allegedly providing evidence that the library of Nissim is a library that has extensive heavy chain repertoires and unique light chain sequence. Therefore, the Examiner alleges that it is *prima facie* obvious to have altered the constructs of de Kruif by using the "knobs-into-holes" method of Ridgway for the purpose of dimerizing the bispecific scFv constructs of de Kruif, and to arrive at the bispecific antibodies of the present invention.

A prima facie case of obviousness has not been established.

The Applicants respectfully to submit that in order to establish a prima facie case of obviousness, three basic criteria must be met:

1) the references when combined must teach or suggest all of the claim limitations;

> 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art; and
>
> 3) there must be a reasonable expectation of success.

MPEP 706.26(j).

Applicants respectfully submit that the Examiner has, in the least, failed to provide a motivation to combine the references.

The Federal Circuit has recently caution against the application of hindsight to reach an obviousness rejection:

> To reach a non-hindsight driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, the Board must provide some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.

In re Kahn, 441 F.3d 977, 987 (Fed. Cir. 2006). Although the Federal Circuit notes that such a suggestion need not be explicit in the art, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Id. (citing to In re Lee, 277 F.3d 1338, 1343-46 (Fed. Cir. 2002) and In re Rouffett, 149 F.3d 1350, 1355-59 (Fed. Cir. 1998). Here, the Examiner has gathered a series of elements from a series of references, and combined them in such a fashion as to allegedly render obvious the claim invention. But what the Examiner has failed to provide is a motive to combine these threads prior to the instant invention.

The Examiner cited Merchant as allegedly disclosing Nissim teaches a library of binding domains comprising common light chains. Then the Examiner argues that de Kruif teaches bi-specific antibodies, and one of the libraries that de Kruif suggests could be used to generate bispecific antibodies is the Nissim library. Although de Kruif discloses, as a possible source of binding domains in a list of sources, the Nissim

library, de Kruif attaches no particular significance to using the same light chain in binding domains. Further, de Kruif does not suggest that both binding domains in a bispecific antibody should be derived from the same library, let alone both be derived from the Nissim library in particular. Thus, de Kruif does not teach an advantage of using a common light chain; in fact, by providing a list of exemplary libraries, de Kruif implies that using a common light chain is irrelevant. Therefore, de Kruif provides no particular motivation to select Nissim.

Further, Nissim doesn't teach bispecific antibodies, Nissim characterizes their library as comprising multispecific antibodies following concentration. Nissim's reference to scFvs forming dimers, i.e., bispecific antibodies as in the instant invention, follows behind an "although" in a sentence distinguishing another paper by another group or as a minor peak in Fig. 7. Thus, Nissim teaches away from bispecific antibodies, if anything.

Although the Examiner correctly observes that Ridgway taught the knobs-into-holes method of heterodimerization, the Examiner provides no reason to combine the teaching of Ridgway with the teaching of de Kruif. de Kruif developed a means of providing for heterodimerization, why would anyone look farther and try a different means of heterodimerization? The Examiner has provided no motivation for one skilled in the art to abandon or supplement the teaching of de Kruif. The Examiner is picking and choosing, from a large body of art, the elements that comprise the Applicants' invention, especially as regards to claims 54-63. One skilled in the art would have no motivation to begin with de Kruif and then jump to the Nissim library; and the Nissim library only, using neither the co-listed Hoogenboom nor de Kruif libraries; to select two binding domains comprising the same light chain; as disclosed by Merchant, not directly by Nissim; and then, in spite of the teachings of heterodimerization provided by de Kruif, to reach out and grab Ridgway to provide an additional, or replacement, means of heterohybrization. The Examiner is stringing together four different references to arrive

at the claimed invention without any apparent motivation other than that provided by the instant invention via hindsight.

Additionally, the instant invention and application describes a strategy which serves to enhance the formation of a desired heteromultimeric bispecific antibody from a mixture of monomers. To accomplish this, the instant invention both engineers an interface between a first and second polypeptide for hetero-oligomerization, and the instant invention also provides a common variable light chain to interact with each of the variable heavy chain regions of the bispecific antibody. Using a common variable light chain, or a pair of light chains with at least 98% sequence identity, thereby reduces the number of monomers that must correctly pair to form the antigen binding domains. This enhances the yield of the desired heteromultimer (e.g., Fig 1C) over undesired heteromultimers and homomultimer (e.g. Fig. 1A). This advantage is not taught by Nissim; they derive no particular advantage by using the same light chain in their scFvs. Nissim devotes little, if any, discussion to the light chain sequence used in their publication. Similarly, de Kruif does not discuss using a single light chain and does not teach an advantage of using a single light chain. The silence of the Nissim and de Kruif publications actually argues in support of the surprising nature of the advantage of using a single light chain of the instant invention. Thus, any additional teachings of Ridgway do not affect the patentability of the instant invention.

The Examiner has gathered together a group of disparate elements of the instant invention from a variety of references and tried to tie them together. But the Examiner has provided no motivation to take all these individual and disparate teachings and tie them together to form the instant invention. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Applicants acknowledge the rejection of claims 47-63 under 35 U.S.C. § 103(a) as being unpatentable over de Kruif, *supra*, as evidenced by Merchant, *supra* in view of Ridgway (of record) and further in view of Hu, *supra*.

The Examiner relies on the combination of de Kruif and Ridgway as discussed above. The Examiner than notes that the above combination fails to teach bispecific antibody constructs where the non-naturally occurring disulfide bond is between the C_H3 rnultimerization domains of the first and second polypeptides. However, the Examiner notes that Hu teaches that single chain Fv constructs can be made divalent by fusing the single chain antibody chains with C_H3 regions; and also teaches the "flex minibody' in which the C_H3 is fused to a hinge region, which contains cysteines for the formation of disulfide bonds, which further stabilize the dimer. The Examiner alleged that it therefore would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified de Kruif's bispecific antibodies to have a C_H3 multimerization domain with knobs-and-holes mutations as taught by Ridgway, and further to have added hinge region to the C_H3 region so that disulfide bonds could form between the heterodimers.

The Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness for the reasons given above. Applicants respectfully submit that in this rejection, as in the one above, the Examiner has, in the least, failed to provide a motivation for combining the references.

Hu teaches a means of dimerizing scFvs via recombinantly attached C_H3 domains. In the rejection, in addition to describing the technology of de Kruif (together with Nissim and Merchant) together with Ridgway, the Examiner notes that Hu describes a method to drive dimerization of single chain binding regions with C_H3 domains and added cysteines to allow the formation of disulfide bridges. In this rejection, the Examiner has brought in an element of yet another reference, Hu, but without providing a motivation to combine Hu with the first three references, let alone combine the disparate elements of the first three references, other than the motivation provided by the instant invention via hindsight. Just considering the added reference, the Examiner has provided no motivation for supplementing the teachings of de Kruif and/or Ridgway. de Kruif and Ridgway both successfully and individually provide

methods of dimerization. One skilled in the art would have no reason to look farther and engineer in the cysteine residues facilitating disulfide bond formation taught by Hu to the methods taught by either de Kruif or Ridgway.

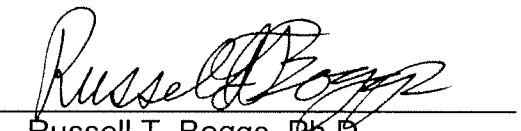
Additionally, as set forth above, the instant inventors describe a strategy which serves to enhance the formation of a desired heteromultimeric bispecific antibody from a mixture of monomers. To accomplish this, the instant invention both engineers an interface between a first and second polypeptide for hetero-oligomerization, and also provides a common variable light chain to interact with each of the variable heavy chain regions of the bispecific antibody. Using a common variable light chain, or a pair of light chains with at least 98% sequence identity, thereby reduces the number of monomers that must correctly pair to form the antigen binding domains. This enhances the yield of the desired heteromultimer (e.g., Fig 1C) over undesired heteromultimers and homomultimer (e.g. Fig. 1A). This advantage is not taught by Nissim; they derive no particular advantage by using the same light chain in their scFvs. Similarly, de Kruif does not discuss using a single light chain and does not teach an advantage of using a single light chain. As noted above, the silence of the Nissim and de Kruif publications actually argues in support of the surprising nature of the advantage of using a single light chain of the instant invention. Thus, any additional teachings of Ridgway and Hu do not affect the patentability of the instant invention.

The Examiner is picking and choosing the elements that comprise the Applicants' invention from a large body of art. But the Examiner has provided no motivation to take all these individual and disparate teachings and tie them together to form the instant invention. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

Applicant believes that this Response has addressed all items in the Office Action and now places the application in condition for allowance. Accordingly, favorable reconsideration and allowance of claims 47-52 and 54-63 at an early date is solicited. No fee is believed due with this response. Nevertheless, the Commissioner is hereby authorized to charge any fee that may be due in connection with this and the attached papers, or with this application during its entire pendency to or to credit any overpayment to Deposit Account No. 08-1641. . Should any issues remain unresolved, the Examiner is invited to telephone the undersigned.

Respectfully submitted,
HELLER EHRMAN LLP

By: 
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